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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/28, 9/30, 9/32, 9/34, 9/36, 9/38, 9/42 — A1

(11) International Publication Number: WO 99/25323

(43) International Publication Date: 27 May 1999 (27.05.99)

(21) International Application Number: PCT/US98/24195

(22) International Filing Date: 13 November 1998 (13.11.98)

(30) Priority Data:
08/970,489 14 November 1997 (14.11.97) US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: OMEPRAZOLE FORMULATION

(57) Abstract

A pharmaceutical composition of omeprazole for oral administration is described which consists essentially of (a) a pellet comprising an inert core component, a therapeutically effective amount of omeprazole, a surface active agent, a filler, a pharmaceutically acceptable alkaline agent and a binder; and (b) a single layer of coating on said pellet which comprises a layer of an enteric coating agent.

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OMEPRAZOLE FORMULATION

BACKGROUND OF THE INVENTION:

The present invention relates to a stable formulation of omeprazole. It is well known that omeprazole is sensitive to acidic conditions and the after contact with an acid, omeprazole will degrade and will not function in its intended manner. Initially, alkaline materials were added to a core of omeprazole and later an enteric coating was applied over the core to prevent the omeprazole from contacting the acidic pH conditions of the stomach. This approach is satisfactory if the product is administered within a short time after it is manufactured but if the product is stored under ambient conditions, the acidic residue of the enteric coating appears to degrade the omeprazole before it is administered to a patient. To solve this problem, the prior art has used a separate layer of a coating agent to coat a pellet core which contains omeprazole and an alkaline material which is thereafter coated with the enteric coating. This technique is described in U.S. 4,786,505.

This dual layer coating technique requires the application of two separate functional coating operations which increases the length of the manufacturing process and the cost of the product. The applicants have surprisingly discovered a coating system which avoids the need to use a coating layer to separate the omeprazole core from the enteric coating layer in an omeprazole dosage form. The separate coating system is based on the combined use of an enteric coating agent which is applied to pellet cores of omeprazole as a suspension in an suitable solvent.

SUMMARY OF THE INVENTION

The present invention provides a novel dosage form of omeprazole which consists essentially of:

(a) a pellet comprising an inert core component, a therapeutically effective amount of omeprazole, a surface active agent, a filler, a pharmaceutically acceptable alkaline agent and a binder; and

(b) a single layer of coating on said pellet which comprises a layer of an enteric coating agent.

Accordingly, it is a primary object of this invention to provide a pharmaceutical dosage formulation of omeprazole which is stable upon prolonged storage, is stable when administered to a patient and is capable of providing the desired therapeutic effect.

It is also an object of this invention to provide a pharmaceutical dosage form of omeprazole which is bioequivalent to dosage forms of omeprazole which have an intermediate layer of an inert coating material.

It is also an object of this invention to provide a stable dosage form of omeprazole which may be produced without the need to provide an intermediate coating layer that separates the omeprazole containing core from the enteric coating layer.

These and other objects of the invention will become apparent from a review of the appended specification.

DETAILED DESCRIPTION OF THE INVENTION

The omeprazole formulation of the invention is preferably based on pellets having a core forming inert component which may comprise a starch or sugar sphere such as non-pareil sugar seeds having an average size of from 14 to 35 mesh, preferably about 18 to 20 mesh. The core forming inert component is coated with a formulation which comprises omeprazole, a surface active agent, a filler, an alkaline material and a binder,

which are collectively referred to hereafter as the drug layer composition. The core forming inert component is employed at 1:1 to 5:1 and preferably from 2:1 to 3:1 weight ratio to the drug layer composition.

The omeprazole may comprise from 20 to 70wt% and preferably 40 to 50wt% of the drug layer composition.

The surface active agent may be any pharmaceutically acceptable, non-toxic surfactant. Suitable surface active agents include sodium lauryl sulfate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80 and the like.

The surface active agent may be present at a level of from 0.1 to 5wt% and preferably 0.25 to 2.5wt% based on the total weight of the drug layer composition.

The alkaline material is selected from the group consisting of the sodium, potassium, calcium, magnesium and aluminum salts of phosphoric acid, carbonic acid, citric acid and aluminum/magnesium compounds such as $Al_2O_3 \cdot 6MgO \cdot CO_2 \cdot 12H_2O$, $(Mg_6Al_2(OH_{1-6}C0_3 \cdot 4H_2O)$, $MgO \cdot Al_2O_3 \cdot 2SiO_2 \cdot nH_2O$ where n is a whole integer of 2 or more. In addition the alkaline material may be selected from the group consisting of antacid materials such as aluminum hydroxides, calcium hydroxides, magnesium hydroxides and magnesium oxide. The alkaline agent may be present at a level of 1 to 20wt% based on the total weight of the coating composition, depending on the relative strength of the alkaline material. If the preferred disodium phosphate alkaline agent is employed, a level of from 1 to 10wt% and preferably 4 to 7wt% based on the weight of the drug layer composition may be employed.

The binder may be any pharmaceutically acceptable, non-toxic pharmaceutically acceptable binder.

The binder is preferably a water soluble polymer of the group consisting of polyvinyl alcohol,

polyvinylpyrrolidone, methylcellulose, hydroxypropyl cellulose, hydroxymethyl cellulose and the like. A water soluble binder is preferred which is applied from an aqueous medium such as water at a level of from 0.1 to 5wt% and preferably from 0.25 to 3wt% of binder based on the total weight of the drug layer composition.

A filler is added to the drug layer. Sugars such as lactose, dextrose, sucrose, maltose, microcrystalline cellulose and the like may be used as fillers in the pellet coating composition. The filler may comprise from 20 to 70wt% and preferably 40 to 50wt% based on the total weight of the drug layer composition.

The enteric coating agent may comprise a acid resisting material which resists acid up to a pH of above about 5.0 or higher which is selected from the group consisting of cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, Eudragit L (poly(methacrylic acid, methylmethacrylate), 1:1 ratio; MW (No. Av. 135,000 - USP Type A) or Eudragit S (poly(methacrylic acid, methylmethacrylate, 1:2 ratio MW (No. Av. 135,000 - USP Type B) and mixtures thereof.

The enteric coating agent may also include an inert processing aid in an amount from 10 to 80wt % and preferably 30 to 50wt% based on the total weight of the acid resisting component and the inert processing aid. The inert processing aids include finely divided forms of talc, silicon dioxide, magnesium stearate etc. Typical solvents which may be used to apply the acid resisting component-inert processing aid mixture include isopropyl alcohol, acetone, methylene chloride and the like. Generally the acid resistant component-inert processing aid mixture will be applied from a 5 to 20wt% of acid resisting component-inert processsing aid mixture based on the total weight of the solvent and the acid resistant component-inert processing aid.

The cores are formed by spraying the non-

pareil seeds with an aqueous or non-aqueous suspension which contains the alkaline agent, the omeprazole, the surface active agent and the binder. The suspension medium may comprise any low viscosity solvent such as water, isopropyl alcohol, acetone, ethanol or the like. When fluids such as water are employed, this will usually require a weight of fluid which is about seven times the weight of the dry components of the coating composition.

After the cores are dried, the cores are coated with the enteric coating agent. A color imparting agent may be added to the enteric coating agent mixture or a rapidly dissolving seal coat containing color may be coated over the enteric coating agent layer provided that the seal coat is compatible with and does not affect the dissolution of the enteric coating layer.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

EXAMPLE 1

Active pellets of omeprazole are formed by placing sugar spheres in a fluidized bed coater and spraying a suspension containing omeprazole onto the sugar spheres. The formulation for making the active pellets has the following composition:

povidone, USP (Plasdone K90)	4.5g
sodium lauryl sulfate, NF	10.6g
lactose anhydrous, NF	427.7g
disodium phosphate, NF	51.3g
omeprazole, USP (micronized)	427.7g
purified water, USP	3336.0g

The povidone, lactose anhydrous, disodium phosphate and the purified water are mixed with a mechanical mixer until the materials are dissolved. Then

the sodium lauryl sulfate is added to the mixture with gentle stirring to avoid the formation of excess foam until it dissolves completely. At that time the micronized omeprazole is added to the mixture and gentle stirring is continued until the micronized omeprazole is completely dispersed.

2500.0g of non-pareil sugar spheres (USPXII) (18/20 mesh) are placed in the fluidized bed coater and the suspension containing the omeprazole is coated at a product temperature of 35-45°C; an atomization pressure of 1.5 - 3.0 bar and a pump rate of 2-50ml/minute, starting with a slow rate of pumping to avoid agglomeration and increasing the rate of pumping consistent with the avoidance of the formation of agglomerates.

After coating is complete the pellets are dried at a temperature of 50°C until the loss on drying is less than 2.5wt% The pellets are then screened through a #14 mesh screen and coated with the following enteric coating formulation:

hydroxypropylmethylcellulose phthalate, NF	258.1g
cetyl alcohol, NF	12.9g
talc, USP	129.0g
isopropyl alcohol, USP*	1663.0g
acetone, NF*	1663.0g

*evaporates during processing

The hydroxypropylmethylcellulose phthalate and the cetyl alcohol are mixed with the isopropyl alcohol and the acetone with agitation until all of the materials are dissolved. The talc is dispersed with agitation in this solution. One kilogram of the active pellets are placed in a fluidized bed coater and all of the enteric coating mixture is applied using the coating conditions that were used to form the active pellets. The enteric coated pellets are then placed into No."2",

hard gelatin capsules containing pellets which are equivalent to 20mg of omeprazole.

The capsules were evaluated for stability as follows:

Dissolution stability:

After acid treatment for 2 hours in 500ml of 0.1N HCl solution at 37°C, the test samples were tested according to the USP XXII dissolution test (type 1, basket) at 100rpm, at 37° in phosphate buffer medium, USP XXII, at pH 6.8 to determine the percent of the drug dissolved versus time. The following results were obtained:

Time (min)	Percent Dissolved initial	40°C/75%RH/1mo	40°C/75%RH/2mo	40°C/75%RH/3mo
10	87	76	95	93
20	90	88	96	95
30	90	86	95	94
60	86	81	91	89

Chemical and Acid Resistance Stability:

The acid resistance study was conducted by using the USP XXII dissolution test (type 1, basket), 100rpm, 37°C.,in a aqueous solution of hydrochloric acid at pH 1.0. The following results were obtained:

	initial	40°C/75%RH/1mo	40°C/75%RH/2mo	40°C/75%RH/3mo
potency (% of LC)	101%	101%	100%	100%
acid resistance (% of LC)	97%	100%	100%	99%

A biostudy was carried out to compare the product of Example 1 with Prilosec brand of omeprazole (Ref. Mean) in humans. The following results were obtained in fasting humans:

	Example 1 Mean	%CV	Ref. Mean	%CV	Geometric ratio	90%Confid.Interv. low.lim	upp. lim
Cmax	134.50	61.46	133.46	60.11	0.964	72.47%	128.19%
AUC 0~t	224.38	68.94	214.61	66.24	1.040	96.08%	112.63%
AUC 0~8	230.87	65.78	220.54	64.76	1.052	97.42%	113.62%
Tmax	2.33	39.90	1.92	44.93	1.232		

All of the components which are used in the present invention are used in amounts which are effective for the intended purpose for which the component is employed.

While certain preferred and alternative embodiments of the invention have been set forth for purposes of disclosing the invention, modifications to the disclosed embodiments may occur to those who are skilled in the art. Accordingly, the appended claims are intended to cover all embodiments of the invention and modifications thereof which do not depart from the spirit and scope of the invention.

Claims:

1. A stable pharmaceutical composition of omeprazole for oral administration which consists essentially of:
(a) a pellet comprising an inert core component, a therapeutically effective amount of omeprazole, a surface active agent, a filler, a pharmaceutically acceptable alkaline agent and a binder; and
(b) a single layer of coating on said pellet which comprises a layer of an enteric coating agent.

2. A pharmaceutical composition of omeprazole as defined in claim 1 wherein the alkaline material is selected from the group consisting of the sodium, potassium, calcium, magnesium and aluminum salts of phosphoric acid, carbonic acid and citric acid.

3. A pharmaceutical composition of omeprazole as defined in claim 1 wherein the alkaline material is selected from the group consisting of aluminum hydroxides, calcium hydroxides, magnesium hydroxides and magnesium oxide.

4. A pharmaceutical composition of omeprazole as defined in claim 1 wherein the acid resistant component is selected from the group consisting of cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, co-polymerized methacrylic acid/methacrylic acid methyl esters.

5. A pharmaceutical composition of omeprazole as defined in claim 1 wherein the enteric coating agent also includes an inert processing aid.

6. A pharmaceutical composition of omeprazole as defined

in claim 1 wherein the enteric coating agent around the core includes from 10 to 80wt% of and inert processing aid.

7. A pharmaceutical composition of omeprazole as defined in claim 1 which includes a sodium lauryl sulfate as the surface active agent.

8. A pharmaceutical composition as defined in claim 1 wherein the core contains a non-pareil sugar seed.

9. A pelleted pharmaceutical dosage formulation which consists essentially of:
(a) a core comprising a non-pareil sugar seed coated with drug layer composition comprising omeprazole, a binder, an alkaline agent, a filler and a surface active agent; and
(b) an enteric coating agent around said core, said enteric coating comprising hydroxypropylmethyl cellulose phthalate and talc.

10. A pelleted pharmaceutical dosage formulation as defined in claim 9 wherein the alkaline agent is disodium phosphate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/24195

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 9/28,9/30, 9/32, 9/34, 9/36, 9/38, 9/42,
US CL : 424/474, 475, 476, 477, 479, 480, 481, 482
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/474, 475, 476, 477, 479, 480, 481, 482

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 5,753,265 A (BERGSTRAND et al.) 19 MAY 1998, col. 6, lines 35-53, lines 50-58, col. 7, lines 10-27, col. 10, line 60 and col. 8, lines 30-65.	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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